Supplementary Information for:

Safety and therapeutic activity of BAY1436032 in IDH1-mutant solid tumors: Phase I study results

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SUPPLEMENTARY METHODS

Study design

Evaluation of dose-limiting toxicities

The DLT evaluation period was defined as the first 21 days of treatment (i.e., Cycle 1; C1). If no DLT was observed during the evaluation period within a given cohort, then the daily dose could be increased by a maximum of 100% in the subsequent cohort provided that ≥grade 2 drug-related toxicities were not observed in 2 or more subjects. If during C1 of a given cohort ≥2 subjects experienced ≥grade 2 drug-related toxicities, or at least 1 subject experienced a DLT, then the daily dose could be increased by a maximum of 50% in subsequent cohorts. In the event of a DLT, Bayesian dose-DLT modeling was to be performed to help guide dosing decisions (1); in this case, the maximum dose predicted to yield a DLT rate of ≤25% was to be selected as the best dose for the next cohort.

Drug administration

Subjects in dose escalation were instructed to take study medication 1 hour before or 2 hours after a meal or snack. After implementation of an amendment during dose expansion, subjects were instructed to take study medication within 30 minutes after a meal. BAY1436032 was found to exhibit similar PK when administered either 1 hour before or 2 hours after a meal or snack, or within 30 minutes after a meal.

Assessments

Safety

Cardiac function was assessed with triplicate 12-lead electrocardiograms at screening, C1-D1 (pre-dose and 2 hours post-dose), C1-D2 (pre-dose), C1-D15 (pre-dose and 2 hours post-dose), D1 of every subsequent cycle (pre-dose), and at treatment end.

Pharmacokinetics

In dose escalation, plasma samples were collected at the following time points and stored frozen for PK assessment: C1-D1: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 hours post-dose (the evening dose of BAY1436032 on C1-D1 was withheld); C1-D8: pre-dose; and C1-D15: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12 hours post-dose. In dose expansion, detailed PK profiling was performed in a subset of subjects using collection time points identical to those indicated above for dose escalation, but with the addition of C≥2-D1 (pre-dose) samples. For another subset of subjects in dose expansion, less detailed PK sampling was performed at the following time points: C1-D1: pre-dose, 2, 4, 8, 12 hours post-dose; C1-D8: pre-dose; C1-D15: pre-dose, 2, 4, 8, 12 hours post-dose; and C≥2-D1: pre-dose.

Quantitative analysis of BAY1436032 (free acid) in plasma was determined using a fully validated method after protein precipitation with acetonitrile/0.4 mM ammonium acetate (pH 3, 80:20, v/v) containing the internal standard, followed by separation employing high-pressure liquid chromatography-tandem mass spectrometric detection (LC-MS/MS). The method validation and sample analysis were performed in compliance with the pertinent guidelines on Bioanalytical Method Validation of FDA (2001) and EMA (2011). Samples were stored at or below -15°C prior to testing. Maximum drug concentration (C_{max}), area under the concentration versus time curve

from time 0 to 12 h ($AUC_{(0-12)}$), and AUC from time 0 to 24 h ($AUC_{(0-24)}$) were calculated using the model-independent (compartment-free) method. Dose proportionality was evaluated by performing explorative analyses of variance (ANOVA) on the log-transformed dose-adjusted values of C_{max}, $AUC_{(0-12)}$ and $AUC_{(0-24)}$, calculated from single and continuous BID dosing PK profiles.

For PK food-effect assessment in a subset of subjects in dose expansion, plasma samples were collected after single doses of BAY1436032 on C1-D(-)2 (under fed conditions) and on C1-D1 (after an overnight fast of at least 8 hours) at the following time points: C1-D(-)2: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 hours post-dose (the evening dose of BAY1436032 on C1-D(-)2 was withheld and BAY1436032 was not administered on C1-D(-)1); C1-D1: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 hours post-dose (the evening dose of BAY1436032 on C1-D1 was withheld).

In order to evaluate a potential food-effect, BAY1436032 C_{max} and $AUC_{(0-24)}$ after a single dose on C1-D(-)2 (following consumption of standard high-fat, high-caloric meal), and C_{max} and $AUC_{(0-24)}$ on C1-D1 (after overnight fasting), were compared. The logarithms of C_{max} and $AUC_{(0-24)}$ were analyzed using a mixed-effect model, including food as a fixed-effect, and subject as a random-effect, in the model. Based on the analyses, point estimate (least square means) and 90% confidence intervals of the difference between the high-fat/high-caloric meal and fasting were calculated using the intra-individual standard deviation for C_{max} and $AUC_{(0-24)}$. The estimate and confidence limits were then exponentiated back to the original scale. In order to evaluate the impact of food on PK exposure in practice, BAY1436032 C_{max} and $AUC_{(0-24)}$ were determined on C1-D15 after multiple dose administration at 1500 mg BID and compared between subjects treated 1 hour before or 2 hours after a meal or snack to those taking BAY1436032 within 30 minutes after a meal.

Pharmacodynamics

For quantification of R-2HG, plasma samples were collected at the following time points and stored frozen prior to testing: screening D(-)7; C1-D1: pre-dose, 2, 4, 8, 12 hours post-dose; C1-D8: pre-dose; C1-D15: pre-dose, 2, 4, 8, 12 hours post-dose; C≥2-D1: pre-dose; and at treatment end. The sampling time points described above were implemented via amendment during the study, and a less dense sampling scheme was used for subjects enrolled prior to the amendment.

Plasma R-2HG concentrations were measured by Eurofins (Luxembourg) using a qualified LC-MS/MS method with a lower limit of quantification (LLOQ) of 25 ng/mL. For assay validation purposes, plasma samples from 9 subjects with wt*IDH1* and wt*IDH2* cholangiocarcinoma were tested and showed a median R-2HG level of 44 ng/mL (32–64), and samples from 9 subjects with m*IDH1* cholangiocarcinoma showed a median R-2HG level of 181 ng/mL (43–1016).

Mutational analysis:

***IDH1* testing:** Only subjects with a tumor-associated IDH1-R132X mutation detected by a DNA-based test were eligible for enrollment. Subjects for whom an IDH1-R132X mutation had been detected locally via a DNA-based test were eligible to sign the main study consent form and enter screening and would submit an archival tumor tissue sample for subsequent conformation of m*IDH1* status at a central laboratory. Subjects interested in this study who had not yet been determined to have an IDH1-R132X tumor-associated mutation detected by a DNA-based test signed a pre-screening consent form to allow for DNA-based *IDH1* testing of a tumor sample at a central

laboratory. If the central laboratory detected an IDH1-R132X mutation, the subject was eligible to sign the main study consent form and enter screening.

The Qiagen therascreen® IDH1/2 kit was used as an investigational *in vitro* diagnostic device to identify IDH1-R132X mutations at a central laboratory for subjects with glioma, ICC, and CS. In cases where therascreen® testing failed, *IDH1* Sanger sequencing was performed at the central laboratory. Subjects with tumor types other than glioma, ICC, or CS who were enrolled based on local *IDH1* test results had confirmatory central testing performed via *IDH1* Sanger sequencing.

Since *IDH1* mutations initially identified in LGG are known to be retained in recurrent tumors that later appear following therapeutic intervention (2), tumor tissue specimens taken at any time during the course of the disease were accepted for *IDH1* testing.

Next-generation sequencing (NGS): Archival tumor tissue from a subset of 30 subjects was tested for alterations in >300 tumor-associated genes via NGS at Foundation Medicine (Cambridge, MA, USA). Information provided by Foundation Medicine included the allelic frequency and likely pathogenic nature of each alteration identified.

SUPPLEMENTARY RESULTS

Evaluation of food-effect

A preliminary assessment was conducted to evaluate a potential food-effect on BAY1436032 exposure. Subjects (n=9) who were administered BAY1436032 after a high-fat meal or under fasting conditions showed a 1.8-fold (0.9–6.8) average increase in exposure with the high-fat meal. Accordingly, after implementation of an amendment during dose expansion, subjects were instructed to take BAY1436032 within 30 minutes after a meal (fat content not specified), with the intention of increasing exposure of study drug. However, increased exposure was not apparent when BAY1436032 was administered within 30 minutes of a meal in which the fat content was not specified (data not shown).

Mutational analysis

Retrospective mutational analysis of a variety of tumor-associated genes was performed via NGS on archival tumor tissue obtained from a subset of 30 m*IDH1* subjects (LGG n=11; GBM n=10; ICC n=8 and OTT n=1) (**Suppl. Table S12**). In m*IDH1* LGG, literature reports have identified molecular differences between subtypes, with mutations in the telomerase reverse transcriptase (*TERT*) promoter and capicua (*CIC*) being associated with oligodendroglioma, and mutations in tumor protein 53 (*TP53*) and alpha thalassemia/mental retardation syndrome X-linked (*ATRX*) being associated with astrocytoma (3). Consistent with expectations, 3/11 of the m*IDH1* LGG subjects included in the mutational analysis had a diagnosis of oligodendroglioma, and all 3 were found to be mutant for *TERT* and *CIC*, but wild-type for *TP53*. Each of the 8 other LGG subjects included in the analysis had alterations in *TP53* but were wild-type for *TERT* and *CIC*; 5 of these subjects also had alterations in *ATRX*. None of the 4 LGG subjects who experienced an OR could be included in this limited mutational analysis due to lack of tumor tissue. For the m*IDH1* ICC subjects

included in this analysis, alterations were detected in *KRAS* and *ATM* (each in 25%; 2/8), as well as *NRAS*, *TP53*, *TERT*, *RBM10*, *PBRM1* and *MAP3K1* (each in 13%; 1/8). Prior molecular analysis of m*IDH1* ICC identified co-mutations in *PBRM1* (13%; 4/30), *TP53* (4%; 4/93), *KRAS* (2%; 2/97) and *NRAS* (0%; 0/70) (4).

SUPPLEMENTARY TABLES

Supplementary Table S1. Outcome of subjects who were still on treatment at the time of data cutoff.

Subject information			Clinical outcome as of data cutoff[1]		Outcome since data cutoff
Age, sex	**Tumor type**	**Start date (dose)**	**Best response**	**PFS (months)**	
48, M	LGG	Dec 2016 (1200 mg BID)	CR	22.0	On study as of Aug 2020: Ongoing CR
45, F	LGG	March 2018 (1500 mg BID)	PR	6.8	On study as of Aug 2020: Ongoing PR
59, M	LGG	June 2018 (1500 mg BID)	SD	4.1	On study as of Aug 2020: Ongoing SD
60, M	LGG	June 2018 (1500 mg BID)	SD	4.1	Off study: PD Oct 2019
67, F	LGG	July 2018 (1500 mg BID)	SD	4.1	On study as of Aug 2020: Ongoing SD
52, F	GBM	Jan 2018 (1500 mg BID)	SD	6.6	Off study: PD Nov 2018
51, M	GBM	March 2018 (1500 mg BID)	SD	7.4	Off study: Death (not attributed to study drug) Sept 2019
63, M	ICC	Dec 2017 (1500 mg BID)	SD	9.7	Off study: PD June 2019

BID: twice-daily; CR: complete response; GBM: glioblastoma; ICC: intrahepatic cholangiocarcinoma; LGG: lower-grade glioma; PD; progressive disease; PFS: progression-free survival; SD: stable disease

[1] Data cutoff: Nov 8, 2018

Supplementary Table S2. Main pharmacokinetic parameters in plasma following single and continuous BID administration of BAY1436032 in dose escalation.

	C1-D1 (single dose)				
	150 mg (n=4)	**300 mg** (n=4)	**600 mg** (n=6)	**1200 mg** (n=4)	**1500 mg** (n=11)
C_{max} µg/L	1130 (50)	747 (62)	1743 (174)	7564 (52)	4299 (66)
$AUC_{(0-12)}$ µg·h/L	3888 (29)	3303 (66)	6841 (166)	31953 (53)	21123 (70)
$AUC_{(0-24)}$ µg·h/L	4108 (28)	4006 (60)	7655 (155)	34193 (51)	24635 (69)

	C1-D15 (continuous BID dosing)				
	150 mg (n=4)	**300 mg** (n=4)[1]	**600 mg** (n=6)	**1200 mg** (n=3)	**1500 mg** (n=9)
$C_{max\ md}$ µg/L	795 (38)	2440 (58)	3009 (60)	2907 (37)	7830 (43)
$AUC_{(0-12)md}$ µg·h/L	3369 (36)	12305 (53)	11829 (54)	15460 (38)	33380 (56)

Numbers represent geometric mean (CV).

$AUC_{(0-12)}$, area under the concentration versus time curve from time 0 to 12 h after a single dose; $AUC_{(0-12)md}$, AUC from 0 to 12 h after continuous BID dosing; $AUC_{(0-24)}$, area under the concentration versus time curve from 0 to 24 h after a single dose; BID, twice-daily; C_{max}, maximum total drug concentration in plasma after a single dose; $C_{max\ md}$, C_{max} after continuous BID dosing; CV, coefficient of variation; n, number of subjects.

[1] Only 2 subjects were used for $AUC_{(0-12)md}$.

Supplementary Table S3. Plasma R-2HG levels in subjects with intrahepatic cholangiocarcinoma.

Subject information[1]				R-2HG levels (ng/mL)[2]												Clinical outcome	
					C1-D1 (post-dose)												
Age, sex	Tumor type	Dose (mg BID)	IDH1 mutation	Baseline	2 h	4 h	6 h	8 h	C1-D8	C1-D15	C2-D1	C3-D1	C4-D1	C5-D1	C6-D1	Max % inhibition	Best response	PFS (months)
51, M	ICC	1500	R132C	1032													Not valid for efficacy	
60, F	ICC	1500	R132C	1757	1587	1187			**212**							88	Not valid for efficacy	
65, M	ICC	1500	R132C	253	222	185	138	115	**49**	85						81	PD	1.3
69, M	ICC	1500	R132C	528					**273**	357						48		0.7
46, M	ICC	1500	R132C	568						583 [3]	748 [3]					0	PD	1.4
73, F	ICC	1500	R132G	334					**142**	221	241					57	Not valid for efficacy	
45, F	ICC	1500	R132C	242					75	**58**	97					76	PD	1.3
69, M	ICC	1500	R132C	205					**74**		93	260				64	PD	1.4
62, F	ICC	1500	R132C	877					241	204	**129**	2094				85	PD	1.5
48, M	ICC	1200	R132L	1782					719	687	**32**	1206				98	PD	1.7
29, M	ICC	600	R132C	356					352	435	671	984				0	PD	1.4
53, M	ICC	1500	R132G	492					69	109	85	**46**	198			91	SD	2.3
58, M	ICC	1500	R132C	134					**59**	60		79	79	130		56	SD	2.7 [5]
59, M	ICC	1500	R132S	472					**118**	174		165	211	234		75	SD	2.8
74, F	ICC	1500	R132L	214					65	55	128	**49**	61	117	97	77	SD	2.8
63, M	ICC	1500	R132C	431	365	233		107	68	74	61	66	67	**36**	62 [4]	92	SD	9.7 [4]
				Median: 452												Median: 76%		

AE, adverse event; BID, twice-daily; ICC, intrahepatic cholangiocarcinoma; PD, progressive disease; PFS, progression-free survival; SD, stable disease.

[1] Includes all treated ICC subjects from dose escalation and dose expansion. The 3 subjects whose R-2HG levels are depicted in Figure 2 are shaded in grey.

[2] Baseline refers to C1-D1 pre-dose, with the exception of the baseline sample from subject "69, M" which was from a screening visit. The lowest during-treatment R-2HG level detected for each subject is bolded.

[3] Subject missed numerous doses of study drug during C1 due to AE.

[4] Although only data to C6-D1 is shown here, R-2HG data was obtained up to C16-D1 (see Figure 2). PFS was censored (subject was ongoing at data cutoff).

[5] PFS was censored (withdrawal from study by subject)

Supplementary Table S4. Treatment-emergent adverse events occurring in ≥10% of subjects in dose escalation and dose expansion.

Dose escalation							
TEAE	**CTCAE grade**	**150 mg BID** n=4	**300 mg BID** n=4	**600 mg BID** n=6	**1200 mg BID** n=4	**1500 mg BID** n=11	**Total** n=29 (%)
Abdominal pain	Grade 1	0	0	0	1	0	1 (3)
	Grade 2	0	0	0	0	2	2 (7)
Diarrhea	Grade 1	0	0	0	0	3	3 (10)
	Grade 2	0	0	1	1	1	3 (10)
Nausea	Grade 1	0	0	0	0	1	1 (3)
	Grade 2	0	0	1	0	1	2 (7)
Vomiting	Grade 1	1	1	0	0	1	3 (10)
	Grade 2	1	0	0	0	2	3 (10)
Fatigue	Grade 1	0	1	1	1	0	3 (10)
	Grade 2	0	0	0	1	0	1 (3)
Influenza-like illness	Grade 1	0	0	0	0	1	1 (3)
	Grade 2	0	0	0	2	1	3 (10)
Blood bilirubin increase	Grade 1	0	0	0	1	1	2 (7)
	Grade 3	0	0	0	0	2	2 (7)
Dysgeusia	Grade 1	0	1	0	1	1	3 (10)
Headache	Grade 1	0	0	0	1	1	2 (7)
	Grade 2	0	0	1	0	1	2 (7)
Seizure	Grade 2	1	0	0	0	0	1 (3)
	Grade 3	0	1	0	0	0	1 (3)
	Grade 5	0	0	1	0	0	1 (3)
Urinary incontinence	Grade 1	1	0	0	0	0	1 (3)
	Grade 2	1	0	0	1	0	2 (7)
Pruritis	Grade 1	0	1	1	0	1	3 (10)

Dose expansion		
TEAE	**CTCAE grade**	**1500 mg BID** n=52 (%)
ALT increase	Grade 1	4 (8)
	Grade 2	2 (4)
	Grade 3	2 (4)
Lipase increase	Grade 1	3 (6)
	Grade 2	1 (2)
	Grade 3	1 (2)
	Grade 4	1 (2)
Headache	Grade 1	5 (10)
	Grade 2	4 (8)
	Grade 3	2 (4)

Nausea	Grade 1	7 (13)
	Grade 2	1 (2)
	Grade 3	1 (2)
Diarrhea	Grade 1	8 (15)
	Grade 2	1 (2)
Vomiting	Grade 1	5 (10)
	Grade 2	3 (6)
Fatigue	Grade 1	5 (10)
	Grade 2	3 (6)
	Grade 3	1 (2)

ALT, alanine aminotransferase; BID, twice-daily; CTCAE, common terminology for adverse events; n, number of subjects; TEAE, treatment-emergent adverse event.

Supplementary Table S5. Clinical outcome in subjects with lower-grade glioma treated in dose escalation and dose expansion.

Subject information[1]					Clinical outcome		
Age, sex	Tumor type	Escalation or expansion	Dose (mg BID)	IDH1 mutation	Best response	PFS (months)	Best % tumor decrease [4]
38, F	Anaplastic oligoastrocytoma	Escalation	1200	R132H		0.3	
32, F	Diffuse astrocytoma	Expansion	1500	R132H	PD	0.3	
52, F	Anaplastic astrocytoma	Expansion	1500	R132H	PD	0.4	
29, M	Diffuse astrocytoma	Expansion	1500	R132H	PD	0.5	
46, F	Diffuse astrocytoma	Expansion	1500	R132H	PD	0.5	
47, M	Anaplastic astrocytoma	Escalation	600	R132H	PD	0.7	
36, M	Diffuse astrocytoma	Expansion	1500	R132H	PD	0.8	2
54, M	Anaplastic oligodendroglioma	Expansion	1500	R132H	PD	1.1	
45, M	Anaplastic astrocytoma	Escalation	600	R132H	PD	1.3	
30, M	Anaplastic astrocytoma	Escalation	150	R132L	PD	1.3	
59, M	Anaplastic oligodendroglioma	Escalation	300	R132H	SD	1.3 [2]	
50, M	Anaplastic astrocytoma	Escalation	600	R132H	PD	1.4	14
30, M	Anaplastic astrocytoma	Expansion	1500	R132H	PD	1.4	
55, M	Anaplastic oligodendroglioma	Expansion	1500	R132H	PD	1.4	
37, M	Anaplastic astrocytoma	Expansion	1500	R132H	PD	1.4	
39, M	Anaplastic astrocytoma	Expansion	1500	R132H	PD	1.4	
51, M	Anaplastic astrocytoma	Escalation	300	R132H	PD	1.4	
34, M	Anaplastic astrocytoma	Expansion	1500	R132H	PD	1.7	
44, M	Anaplastic astrocytoma	Expansion	1500	R132H	SD	2.1	
46, F	Anaplastic oligodendroglioma	Expansion	1500	R132H	SD	2.1	
34, M	Anaplastic astrocytoma	Expansion	1500	R132C	SD	2.7 [2]	
47, F [5]	Diffuse astrocytoma	Escalation	600	R132H	SD	2.7	
67, M	Anaplastic oligodendroglioma	Expansion	1500	R132H	PR	2.8	72
43, M	Anaplastic astrocytoma	Expansion	1500	R132C	SD	2.8	
43, M	Anaplastic oligodendroglioma	Escalation	300	R132H	SD	2.8	
49, F [5]	Anaplastic astrocytoma	Escalation	1500	R132H	SD	2.8	
51, M	Anaplastic oligodendroglioma	Escalation	300	R132H	SD	3.9 [2]	4
49, F	Anaplastic oligodendroglioma	Expansion	1500	R132H	SD	4.1	
44, M	Oligoastrocytoma	Escalation	1200	R132H	SD	4.1	1
59, M	Anaplastic oligodendroglioma	Expansion	1500	R132H	SD	4.1 [3]	17
67, F	Oligodendroglioma	Expansion	1500	R132H	SD	4.1 [3]	36

60, M	Diffuse astrocytoma	Expansion	1500	R132H	SD	4.1 [3]	33
66, M	Oligodendroglioma	Escalation	1500	R132H	SD	5.5	12
45, M	Anaplastic oligodendroglioma	Expansion	1500	R132S	PR	6.5	65
45, F	Anaplastic astrocytoma	Expansion	1500	R132H	PR	6.8 [3]	99
48, M	Anaplastic astrocytoma	Escalation	1200	R132H	CR	22.0 [3]	97

BID, twice-daily; CR, complete response; LGG, lower-grade glioma; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

[1] Includes LGG subjects from dose escalation and dose expansion who were evaluable for efficacy. Subjects who experienced an objective response are shaded in grey.

[2] PFS was censored (withdrawal by subject)

[3] PFS was censored (subject ongoing at data cutoff)

[4] Results are shown only for subjects with valid baseline and during-treatment tumor assessments who showed a decrease in tumor size during treatment; best % decrease in tumor size experienced up to the point of PD is indicated

[5] Thirty-three out of 35 evaluable LGG subjects had a measurable lesion. The two subjects who did not (47, F and 49, F), are indicated. A measurable lesion per RANO (from which Target lesions are selected) is defined as (1) Contrast enhancing lesions; (2) Minimum size: two perpendicular diameters ≥10 mm (if slice + gap thickness >5 mm, minimum size is 2 times the total); (3) Do not include cavity, cyst, or necrosis in the measurement.

Supplementary Table S6. Clinical outcome in subjects with "other tumor types" treated in dose escalation and dose expansion.

Subject information[1]					Clinical outcome		
Age, sex	Tumor type	Escalation or expansion	Dose (mg BID)	IDH1 mutation	Best response	PFS (months)	Best % tumor decrease [3]
42, M	CS	Expansion	1500	R132C	PD	0.7	
58, M	CS	Expansion	1500	R132G	PD	0.7	
74, M	CS	Expansion	1500	R132S	PD	1.3	
65, M	Appendiceal cancer	Expansion	1500	R132C	SD	1.3 [2]	
58, M	CS	Expansion	1500	R132C	PD	1.4	
33, M	CS	Escalation	1500	R132C	PD	1.4	
81, F	Pancreatic cancer	Escalation	600	R132H	SD	2.3	5
19, F	Adrenocortical cancer	Expansion	1500	R132H	SD	2.6	
32, M	CS	Escalation	150	R132C	SD	3.8	
58, M	CS	Expansion	1500	R132C	SD	5.5	

BID, twice-daily; CS, chondrosarcoma; OTT, other tumor type; PD, progressive disease; PFS, progression-free survival; SD, stable disease.

[1] Includes OTT subjects from dose escalation and dose expansion who were evaluable for efficacy.

[2] PFS was censored (withdrawal by subject)

[3] Results are shown only for subjects with valid baseline and during-treatment tumor assessments who showed a decrease in tumor size during treatment; best % decrease in tumor size experienced up to the point of PD is indicated.

Supplementary Table S7. Clinical outcome in subjects with intrahepatic cholangiocarcinoma treated in dose escalation and dose expansion.

Subject information[1]					Clinical outcome[2]	
Age, sex	Tumor type	Escalation or expansion	Dose (mg BID)	IDH1 mutation	Best response	PFS (months)
69, M	ICC	Expansion	1500	R132C		0.7
65, M	ICC	Expansion	1500	R132C	PD	1.3
45, F	ICC	Escalation	1500	R132C	PD	1.3
46, M	ICC	Escalation	1500	R132C	PD	1.4
69, M	ICC	Expansion	1500	R132C	PD	1.4
29, M	ICC	Escalation	600	R132C	PD	1.4
62, F	ICC	Expansion	1500	R132C	PD	1.5
48, M	ICC	Escalation	1200	R132L	PD	1.7
53, M	ICC	Escalation	1500	R132G	SD	2.3
58, M	ICC	Escalation	1500	R132C	SD	2.7 [3]
59, M	ICC	Escalation	1500	R132S	SD	2.8
74, F	ICC	Escalation	1500	R132L	SD	2.8
63, M	ICC	Expansion	1500	R132C	SD	9.7 [4]

BID, twice-daily; ICC, intrahepatic cholangiocarcinoma; PD, progressive disease; PFS, progression-free survival; SD, stable disease

[1] Includes ICC subjects from dose escalation and dose expansion who were evaluable for efficacy

[2] No subject experienced a decrease in tumor size during treatment (up to the point of PD)

[3] PFS was censored (withdrawal by subject)

[4] PFS was censored (subject ongoing at data cutoff)

Supplementary Table S8. Clinical outcome in subjects with glioblastoma treated in dose escalation and dose expansion.

Subject information[1]					Clinical outcome		
Age, sex	Tumor type	Escalation or expansion	Dose (mg BID)	IDH1 mutation	Best response	PFS (months)	Best % tumor decrease [5]
32, M	GBM	Expansion	1500	R132H	PD	0.4	
36, M	GBM	Escalation	150	R132H		0.7	
53, F	GBM	Expansion	1500	R132H	PD	0.7	
27, M	GBM	Escalation	150	R132H	PD	0.9	
42, M	GBM	Expansion	1500	R132H	SD	1.1 [3]	
43, M	GBM	Expansion	1500	R132X [2]	PD	1.3	
23, F	GBM	Expansion	1500	R132H	PD	1.4	
48, F	GBM	Expansion	1500	R132H	PD	1.4	
45, M	GBM	Expansion	1500	R132H	PD	1.4	
32, M	GBM	Expansion	1500	R132H	PD	1.4	
46, M	GBM	Expansion	1500	R132H	PD	1.4	
40, M	GBM	Expansion	1500	R132H	PD	1.4	
55, M	GBM	Escalation	1500	R132H	SD	4.1	35
52, F	GBM	Expansion	1500	R132H	SD	6.6 [4]	22
51, M	GBM	Expansion	1500	R132H	SD	7.4 [4]	

BID, twice-daily; GBM, glioblastoma; PD, progressive disease; PFS, progression-free survival; SD, stable disease.

[1] Includes GBM subjects from dose escalation and dose expansion who were evaluable for efficacy

[2] The precise IDH1-R132 mutation present was not determined

[3] PFS was censored (subject withdrawal due to AE not associated with disease progression)

[4] PFS was censored (subject ongoing at data cutoff)

[5] Results are shown only for subjects with valid baseline and during-treatment tumor assessments who showed a decrease in tumor size during treatment; best % decrease in tumor size experienced up to the point of PD is indicated

Supplementary Table S9. Best investigator-reported response in dose escalation as determined by RANO or RECIST.

	BAY1436032 dose; mg BID[1]					
Best response	**150** (n=3)	**300** (n=4)	**600** (n=6)	**1200** (n=3)	**1500** (n=10)	**Total** (n=26)
CR	0	0	0	1 (33)	0	1 (4)
PR	0	0	0	0	0	0
SD	1 (33) [2]	3 (75)	2 (33)	1 (33)	7 (70)	14 (55)
PD	2 (66)	1 (25)	4 (67)	1 (33)	3 (30)	11 (42)
PFS rate at 3 months[1]						0.25 (0.08, 0.42)

BID, twice-daily; CR, complete response; n, number of subjects; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

[1] Best response analysis Includes 26 subjects from dose escalation who were evaluable via RANO or RECIST. PFS analysis includes these 26 subjects, in addition to 2 subjects who had clinical progression without radiological assessment and were not included in the best response analysis.

[2] Number of subjects (%).

Supplementary Table S10. Subjects on treatment for >2 years and/or who experienced an objective response.

Baseline information				Prior treatments			BAY1436032 treatment				Clinical outcome				
Age, sex	Diagnosis	IDH1 mutation	Tumor size[1]	N of surgeries	N of rounds of RDT	Prior systemic therapies	Time from last systemic therapy to start of treatment (mo)	Clinical status at study entry	BAY1436032 dose (BID)	On treatment as of August 2020? (total duration)	Best response[2]	DOR (mo)	PFS (mo)	DOT (mo)	Best % tumor decrease[3]
48 M	Anaplastic astrocytoma	R132H	12	1 (C)	1	TMZ	11	PD	1200 mg	Yes (44 mo)	**CR** (SD: C3 PR: C9)	16.6[4]	22.0[4]	22.7[4]	97[4]
45 F	Anaplastic astrocytoma	R132H	26	4 (P)	1	PCV TMZ	33	SD	1500 mg	Yes (29 mo)	**PR** (SD: C3 PR: C9-C11[4])	1.3[4]	6.8[4]	8.2[4]	99[4]
45 M	Anaplastic oligo-dendroglioma	R132S	10	2 (P)	1	TMZ PC	1	PD	1500 mg	No	**PR** (PR: C3-C9)	5.2	6.5	6.8	65
67 M	Anaplastic oligo-dendroglioma	R132H	16, 20	1 (P)	2	TMZ CB	5	PD	1500 mg	No	**PR** (PR: C3)	1.4	2.8	4.5	72
59 M	Anaplastic oligo-dendroglioma	R132H	22	1 (P)	2	PCV TMZ CE	4	PD	1500 mg	Yes (26 mo)	**SD** (SD: C3-C7[4])	NA	4.1[4]	4.9[4]	17[4]
67 F	Oligo-dendroglioma	R132H	10	1 (P)	1	TMZ	11	PD	1500 mg	Yes (25 mo)	**SD** (SD: C3-C7[4])	NA	4.1[4]	4.2[4]	36[4]

C, complete resection; CB, lomustine + bevacizumab; CE, lomustine + etoposide; CR, complete response; DOR, duration of response in months; DOT, duration of treatment in months; Mo, months; NA; not applicable; P, partial resection; PC, procarbazine + lomustine; PCV, procarbazine + lomustine + vincristine; PD, progressive disease; PFS, progression-free survival in months, PR, partial response; RDT, radiotherapy; SD, stable disease; TMZ, temozolomide.

[1] Perpendicular diameter (in millimeters) of target lesion(s) as determined by magnetic resonance imaging

[2] Includes cycle number at which responses were first achieved. Best response achieved is bolded.

[3] Best % decrease in tumor size experienced up to the point of progressive disease, or data cutoff (Nov 8, 2018)

[4] Censored (subject ongoing at data cutoff)

Supplementary Table S11. Best investigator-reported response in dose expansion as determined by RANO or RECIST.

	Tumor type[1]				
Best response	**OTT** (n=7)	**ICC** (n=4)	**GBM** (n=12)	**LGG** (n=22)	**Total** (n=45)
CR	0	0	0	0	0
PR	0	0	0	3 (14)	3 (7)
SD	3 (43) [2]	1 (25)	3 (25)	8 (36)	15 (33)
PD	4 (57)	3 (75)	9 (75)	11 (50)	27 (60)
PFS rate at 3 months[1]	0.19 (0, 0.52)	0.20 (0, 0.55)	0.19 (0, 0.41)	0.31 (0.11, 0.50)	0.25 (0.12, 0.38)

CR, complete response; GBM; glioblastoma; ICC; intrahepatic cholangiocarcinoma; LGG, lower-grade glioma; n, number of subjects; OTT, other tumor types; PD, progressive disease; PFS, progression-free survival; PR, partial response, SD, stable disease.

[1] Best response analysis Includes 45 subjects from dose expansion who were evaluable via RANO or RECIST. PFS analysis includes these 45 subjects, in addition to 1 subject who had clinical progression without radiological assessment and was not included in the best response analysis.

[2] Number of subjects (%).

Supplementary Table S12. NGS

Please see separate table in Excel format

References

1. Tibaldi FS, Beck BHL, Bedding A. Implementation of a phase 1 adaptive clinical trial in a treatment of Type 2 diabetes. Drug Inf J. 2008;42(5):455-65.

2. Johnson BE, Mazor T, Hong C, Barnes M, Aihara K, McLean CY, et al. Mutational analysis reveals the origin and therapy-driven evolution of recurrent glioma. Science. 2014;343(6167):189-93.

3. Schiff D, Van den Bent M, Vogelbaum MA, Wick W, Miller CR, Taphoorn M, et al. Recent developments and future directions in adult lower-grade gliomas: Society for Neuro-Oncology (SNO) and European Association of Neuro-Oncology (EANO) consensus. Neuro Oncol. 2019;21(7):837-53.

4. Boscoe AN, Rolland C, Kelley RK. Frequency and prognostic significance of isocitrate dehydrogenase 1 mutations in cholangiocarcinoma: a systematic literature review. J Gastrointest Oncol. 2019;10(4):751-65.